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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,666	02/15/2002	Tsuneji Suzuki	054160-5060	7720

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,666	SUZUKI ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 12-9-05 is acknowledged.

Claims included in the prosecution are 44-49.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this office action'.

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 44-49 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 (Suzuki et al).

EP teaches benzamide derivative claimed by applicant (see claim 14). Additionally, EP teaches that the active ingredient may be used in general pharmaceutical compositions, and may be prepared with generally used diluents or excipients, such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants. EP also teaches that the pharmaceutical dosage form can be a tablet, pill, powder, solution, suspension, emulsion, granules, capsule, injection or suppository. More specifically, EP teaches the use of calcium carbonate, amino acids, starch, methyl

celluloses, calcium Carmellose, lactose, sugars, stearates, talc, polyethylene glycol, sodium alginate and many other well known excipients (page 46, lines 5- 39). The use of these excipients in combination with claimed benzamide derivative would have been obvious to one of ordinary skill in the art with a reasonable expectation of success, since EP is suggestive of these art known excipients together with the benzamide derivative.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant continues to argue that Suzuki does not teach a benzamide derivative with an excipient, a lubricant, a disintegrants and an amino compound and/or an inorganic base. According to applicant, Suzuki merely provides a general laundry list of additives, such as those at page 46, which may potentially be used for pharmaceutical formulations of any sort. This argument is not persuasive since in the tabletting art, the commonly used additives are a binder to bind the small amounts of the active agent, a disintegrants which enables the tablet to disintegrate in the system, a lubricant, amino compounds and buffering agents such as phosphates. What Suzuki advocates is the use of these in combination with the claimed benzamide derivatives. With regard to applicant's argument that without additional guidance, a person of ordinary skill in the art would not be motivated to prepare the particular formulations claimed by applicant, the examiner points out that instant claims do not recite specific combinations of compounds in specific amounts; In instant claims applicant only lists several compounds which belong to each category as binders, disintegrants etc as Markush members. Thus, the motivation comes from the tabletting art which uses the

excipients, disintegrants, lubricants etc routinely. The examiner cites US 6,380,259 (see col. 11, lines 40-51), 5,455,274 (see col. 14, lines 42-53) and 5,605,889 (see col. 19, Table X) to show that the compounds claimed as Markush members are routinely used in tabletting art. The examiner also cites (5,500,422) which shows the routinely used components in combination with benzamide compounds (see col. 10, line 60 through col. 11, line 4 and Example 68). With regard to the superior properties with respect to the stability of the benzamide derivative against degradation argued by applicant (examples 2-6), the examiner points out that the experiment was conducted with specific components with specific amounts whereas instant claims are drawn to the combination of several components. First of all, as pointed out before, instant 'benzamide derivatives' includes three different compounds and therefore, the results are not commensurate with the scope of the claims (even with regard to the amounts of the excipients). Secondly, each of (ii) and (iii) recite structurally unrelated components (art known excipients) the instant claimed combination of (ii) and (iii) would result in multitudes of combination products and applicants themselves have not shown the unexpected nature of the specific combination on the three different active agents claimed. Thirdly, as pointed out before, the examiner is unable to see how one can say that differences observed are significant (no statistical evaluation was done), let alone 'unexpected'. A careful examination of the results in the Table 1 indicate not much of a difference between the control value (0.18) and others claimed to be providing stability (see for example mannitol (0.21), hydroxypropyl cellulose (0.20), Magnesium stearate (0.22). Furthermore, table 4 shows small differences of about 1 to 1.5 % and it is

unclear whether these differences are statistically significant let alone patentably significant. With regard to the examples showing the effect of polyethylene glycol, the examiner points out once again that these studies were done with a buffer and polyethylene glycol and instant claims 46 and 47 are not drawn to this specific combination and applicant has not shown that polyethylene glycol has the same effect in combination with other components. It is still the position of the examiner that selection of a proper excipients combination and to determine their amounts to obtain the best possible results is a routine experimentation practiced by a skilled artisan.

3. Claims 44-49 are rejected under 35 U.S.C. l03 (a) as being unpatentable over EP 0847 992 in view of the International Cosmetic Ingredient Dictionary and Handbook.

EP described above as teaching pharmaceutical compositions comprising benzamide derivatives. EP teaches the inclusion of many well-known pharmaceutical excipients. EP does not teach the inclusion of each of the specific excipients claimed by Applicant. EP does not specifically teach mannitol or claimed amino compound or organic and inorganic salts. The International Cosmetic Ingredient Dictionary and Handbook is relied upon for the teachings that mannitol as well known binder. Lastly, the Dictionary and Handbook is relied upon for the teaching that inorganic compounds such as sodium bicarbonate, disodium phosphate, potassium bicarbonate and ammonia, as well as amino compounds such as triethanolamine, diethanolamine, diisopropanolamine, and triisopropanolamine, as well as organic acid salts such as sodium fumarate, and trisodium phosphate are all well known pH adjusters. Each of these types of excipients (binders, film formers and pH adjusters) is well known

excipients used in the making of pharmaceutical formulations. Therefore, their inclusion in a pharmaceutical composition, which allows for necessary excipients, is not found to be patentable. The selection of a known material based on its suitability for its intended use is obvious, absent a clear showing of unexpected results attributable to the Applicant's specific selection. One skilled in the art would have been motivated to include the well-known excipients discussed above in the compositions described by EP with a reasonable expectation of success. The motivation to do so lies in the teaching of EP that well known excipients can be included in their formulation. Adjusting the pH of a composition is deemed to be within the skill of the art since that is routinely practiced in the fields of Chemistry and Biochemistry. The criticality of the product produced by dry granulation is unclear since one of ordinary skill in the art would avoid wet granulation process if the moisture leads to the degradation of the active agent. Therefore, this invention as a whole would have been prima-facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicants' arguments with regard to EP. Applicants argue that they have demonstrated that several inorganic and amino compounds enhance the stability of benzamide derivatives and if pH were the only factor involved in stability, then the benzamides of formula (I) which themselves are amino compounds, would not degrade in formulations with neutral excipients such as lactose. Applicants once again point out to the results in Table I. These arguments are not found to be persuasive for the same reasons listed in the above rejection over EP

alone. With regard to the examiner's position on the results in Table I, applicant argues that the examiner has incorrectly considered the data. According to applicant, "The fact, recognized by the Examiner, that the control value and the values for the stability enhancing additives are the same is the unexpected result. Applicants point to page 1, lines 27-36 of Applicants' specification which states that although the benzamide derivatives and pharmaceutically acceptable salts thereof of the present invention are stable per se, they become unstable and decompose markedly over time when combined with (select) additives" commonly used in dosage forms (emphasis added). Therefore, the control value, which represents the benzamide alone, is indicative of a stable condition. The fact that there is no significant difference between the control value and the values for, for example, mannitol (0.2 1), hydroxypropyl cellulose (0.20) and magnesium stearate (0.22) as shown in Table 1 (as the Examiner noted), is proof of the stabilizing effects of these additives under both air-tight and open-air conditions as opposed to the comparatively large values for other additives such as lactose (0.55), com starch (0.39) and titanium dioxide (1 .75), which indicate substantial degradation of the benzamide derivatives.

Applicant pointing to Table 1 results and argues what while some compounds such as corn starch were found to accelerate the rate or decomposition of the benzamide derivative of formula (3), (compound 1), others such as gelatinized starch, magnesium stearate and others stabilize the compound 1. These arguments are not found to be persuasive since a careful examination of the results in the Table indicate not much of a difference between the control value (0.18) and others claimed to be providing stability

(see for example mannitol (0.21), hydroxypropyl cellulose (0.20), Magnesium stearate (0.22). From these values it is unclear to the examiner as to one can argue about unexpected results. Furthermore, formula 1 encompasses three different compounds and it is unclear whether the claimed excipients behave the same way with all three compounds. Prior art teaches the same benzamide compound and is suggestive of various excipients in combination with this compound. Instant invention containing art known additives therefore, is prima facie obvious to one of ordinary skill in the art". These arguments are not found to be persuasive since these do not indicate 'unexpected' nature of the results, but rather a routine experimentation and determination of the selection of a proper combination of excipients, which do not affect the stability of an already stable compound.

4. Claims 44-49 are rejected under 35 U.S.C. 103 (a) as being unpatentable over EP 0847 992 combination with Savastano (5,681,584).

The teachings of EP have been discussed above. EP does not specifically teach excipients such as pregelatinized starch, mannitol, amino acids such as glycine, inorganic salts such as disodium phosphate.

Savastano while disclosing tablet formulations of Benzamide derivatives suggests that excipients such as pregelatinized starch, mannitol, amino acids such as glycine, and inorganic salts such as disodium phosphate be used (col. 7, line 4 through col. 8, line 65).

It would have been obvious to use these excipients in the compositions of EP would have been obvious to one of ordinary skill in the art with a reasonable expectation

of success since the reference of Savastano is suggestive of the use of these excipients with other benzamide derivatives. As pointed out above, adjusting the pH of the composition with acids and bases to obtain the desired pH at which the benzamide derivatives are fully active without degradation is well within the skill of the art.

The references of Tamura (6,107,323) (see tables) Ito (5,500,422) (see columns 10-11) and Remington's Pharmaceutical Sciences, pages 1633-1645 are cited as interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/ S Kishore

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